Antimycobacterials

Introduction

Mycobacteria have a uniquely structured cell wall. They have a plasma membrane, like all cells; then, working from the inside of the cell out, a **very thin peptidoglycan layer** (which is why TB can show up as "weakly Gram positive"—it does have some peptidoglycan layer in its cell wall), followed by an arabinogalactan layer (you don't have to know what an arabinogalactan is), followed by a final **mycolic acid layer** (mycolic acids are large fatty acids that have nothing to do with fungi, even though they have "myco" in the name, which normally implies fungi). It is difficult to kill these things, because there are three defensive layers preventing our antibiotics from getting in. On top of that, these are **intracellular organisms** living in macrophages. And they **grow slowly.** That means "antibiosing" them will take patience (long duration of treatment) and multiple agents.

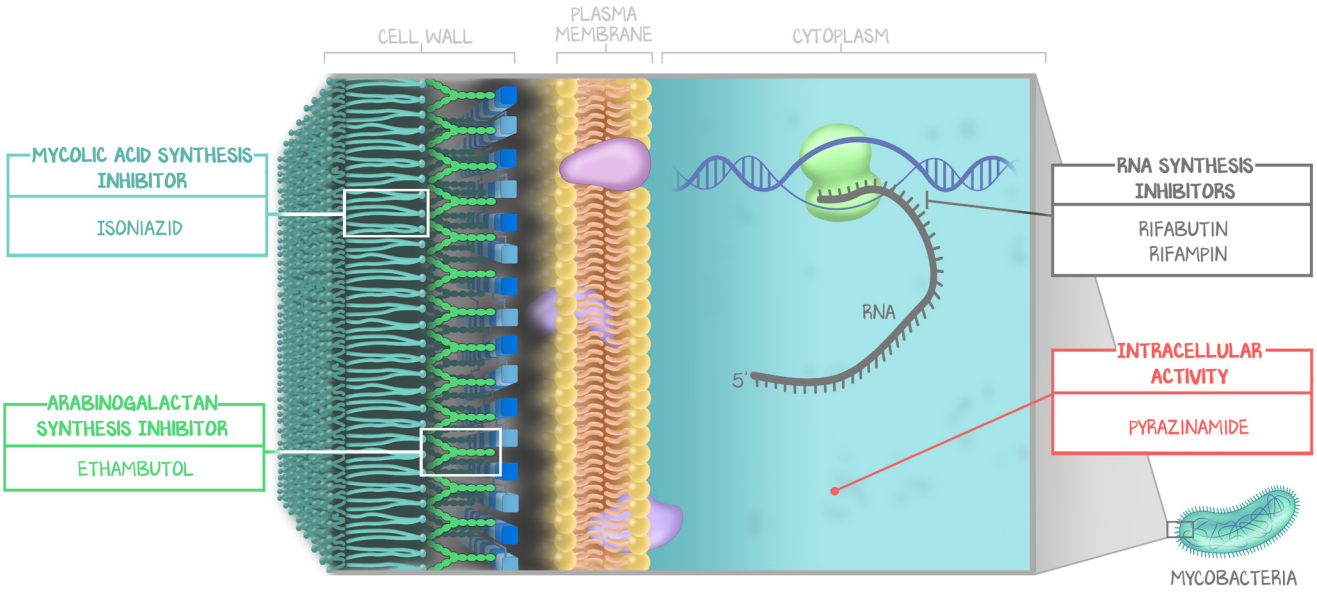

Figure 6.1: *Mycobacterium tuberculosis* Structure and Treatment
Mycolic acid synthesis inhibitors (isoniazid) target the mycolic acid layer. Arabinosyltransferase inhibitors (ethambutol) target the arabinogalactan layer. Rifamycins (rifampin, rifabutin) inhibit RNA polymerase. The cellular mechanism of pyrazinamide is unknown. The order is presented from the outside of the cell, in. However, we want you learning them as RIPE.

You may have noticed that Figure 6.1 is not an exhaustive list of antimycobacterial agents, but instead is limited to the treatment for pulmonary TB. That is intentional. We want you focused on the treatment of *Mycobacterium tuberculosis*, the disease that causes pulmonary TB. We will also discuss treatment of *Mycobacterium leprae* and *Mycobacterium avium-intracellulare* after a lengthy discussion of RIPE for those who are pursuing score augmentation. However, the main focus of the lesson is RIPE. RIPE is the treatment of the regular old susceptible TB that causes pulmonary TB in the United States. We advocate strongly for ignoring alternative agents and multi-drug-resistant TB regimens.

We cover the absolute must-know information about RIPE and the treatment of pulmonary TB, then move into the lower-yield stuff about other mycobacteria and their regimens.

RIPE

The treatment for **active pulmonary TB** is **RIPE**, which stands for Rifampin, Isoniazid, Pyrazinamide, and Ethambutol. The complexities of when the regimen can be changed, when it is acceptable to stop some medications and which ones, is beyond the scope of the basic sciences (rifampin and isoniazid stay for a year, pyrazinamide and ethambutol can come off after 2 months). The treatment of **latent TB** is **isoniazid alone**. What this means is that you are not responsible for choosing the regimen. It's either RIPE or isoniazid. There aren't multiple drugs in each class to choose from; it's always RIPE or isoniazid. So, the questions you are going to get will not be management questions, but questions about **mechanism of action** and **side effects**, as shown in Table 6.1.

DRUG		MECHANISM	SIDE EFFECTS
R	Rifampin	Inhibits DNA-dependent RNA polymerase (transcription inhibitor)	Red body fluids
I	Isoniazid	Inhibits mycolic acid synthesis	Peripheral neuropathy (add B_6 to prevent) Can also cause drug-induced lupus in slow acetylators
P	Pyrazinamide	Unknown	Uric acid stones
E	Ethambutol	Inhibits synthesis of arabinogalactan	Eye-thambutol, red/green color blindness

Table 6.1: RIPE Mechanism of Action and Side Effects
Rifampin causes red body fluids; isoniazid needs B_6 to prevent peripheral neuropathy; pyrazinamide causes uric acid stones; ethambutol causes red/green color blindness.

Rifamycins = Rifampin

The rifamycins are **rifampin** (the standard to use) and rifabutin (the choice for coinfection with HIV and HAART involving protease inhibitors). Rifamycins **inhibit mycobacterial DNA-dependent RNA polymerase**. Resistance develops quickly in the binding site on the RNA polymerase, so it is **never used as monotherapy for TB**. It is also used as *Neisseria meningitidis* **prophylaxis monotherapy** for close contacts. It is famous for **turning body fluids red**, a benign but dramatic effect. It is a **P450 inducer**, so will expedite clearance of some drugs. Ones of import are warfarin (subtherapeutic INR), HIV protease inhibitors (use rifabutin instead of rifampin), and oral contraceptives.

Never use rifampin alone for TB. Use rifampin alone only for close contacts of patients with *Neisseria* meningitis (this is the diagnosis "meningitis," and not the species name "*meningitidis*"). Rifampin turns the body secretions red.

Isoniazid (+ B_6)

Isoniazid **inhibits mycolic acid synthesis**. The mycolic acid layer is the largest and the most peripheral of the cell wall, the "first layer" we encounter. We use this to remember that **isoniazid is always indicated** for treatment of TB—used as monotherapy prophylaxis, monotherapy for latent TB (CXR positive but sputum negative), and always included in the treatment of active TB. Isoniazid is a prodrug, converted to the active form by **catalase-peroxidase** (also called **KatG**). The active metabolite then **inhibits KatA**, which build the mycolic acid. TB is catalase positive in vivo, but catalase negative in the culture because TB has a heat-sensitive catalase. That catalase is KatG. We take advantage of KatG to activate an antibacterial prodrug. Resistance can be developed by **downregulating KatG** (the necessary enzyme to activate isoniazid) or by altering the binding site of the drug of KatA (**mutation**).

Isoniazid causes a **B_6 deficiency**. It competes with B_6 in the renal tubules, forcing an increased elimination of the vitamin. B_6 is a cofactor for the synthesis of neurotransmitters, the heme part of hemoglobin, and for hepatic aminotransferases. Isoniazid induces a B_6 deficiency, which presents as **peripheral neuropathy** (neurotransmitters) and **sideroblastic anemia** (heme synthesis). Isoniazid also is **hepatotoxic**, but not because of the B_6 deficiency. We use the hepatic aminotransferase cofactor as the memory cue for isoniazid's hepatotoxicity, but be careful not to attribute it to the B_6 deficiency. That is because **adding B_6 supplementation** prevents the B_6 deficiency, preventing the peripheral neuropathy and sideroblastic anemia, but does not prevent the risk to the patient's liver. "Isoniazid" should always be written and prescribed as "**isoniazid and B_6.**" There is never a reason not to supplement with B_6, which is why you will see isoniazid written "isoniazid (+B_6)" for the rest of the lesson.

Isoniazid (+B_6) is a dirty drug. It is **hepatically metabolized** via **acetylation**. There are those **slow acetylators** who cannot metabolize isoniazid (+B_6), and toxic levels can accumulate, while **fast acetylators** may clear the drug too quickly, limiting the effect. Most people are **normal acetylators**. The risk of hepatic injury is increased with coadministration of **rifampin** or ingestion of **alcohol**. Since rifampin (or other rifamycins) is standard therapy for TB, there must be cessation of alcohol and close attention paid to liver function. Liver function is monitored with frequent assessments of liver enzymes. Isoniazid (+B_6) also **inhibits P450** enzymes, slowing metabolism of other drugs. Commonly tested is phenytoin.

DRUG	COMPLICATIONS
Isoniazid (+B_6)	Peripheral neuropathy treated with B_6
	Sideroblastic anemia because of B_6 deficiency (most common cause of sideroblastic anemia)
	Causes drug-induced lupus (super-duper rare; not one of the "big 3" discussed in MSK module)

Table 6.2: Isoniazid (+B_6) Complications
Always give B_6 with isoniazid (+B_6) to prevent peripheral neuropathy and sideroblastic anemia. Give isoniazid (+B_6) for latent TB (positive tests, negative sputum), and give isoniazid (+B_6) as part of RIPE for active TB.

If you have to pick one drug on a test regarding TB, and it isn't a side effect question, pick isoniazid (+B_6). If it is a side effect question, pay attention: it could still be isoniazid (+B_6).

Ethambutol

By inhibiting **arabinosyltransferase,** ethambutol prevents the formation of the **arabinogalactan layer**, further weakening the cell wall. It is renally cleared, and those patients with chronic kidney disease have a higher risk of side effects. The most important of these is optic neuritis, which presents with decreased visual acuity and **red/green color blindness**. This can be remembered by thinking of this as "eye-thambutol." Always ensure visual acuity and color testing prior to starting, and test every visit.

Eye-thambutol causes red/green color blindness and changes in vision.

Pyrazinamide

The mechanism is unknown. It is a prodrug that is hydrolyzed to the active compound. It can **cause gout** by **retaining uric acid** or worsen **hepatotoxicity** of the other TB meds. Most of the benefit from pyrazinamide is lost after 2 months, so an entire duration is not required if there are side effects. The most important thing for your learning is to recognize that pyra-zin-amide for TB is different than pyri-meth-amine for *Toxoplasma*. They both look similar if you don't pay attention.

Alternative Regimens

Streptomycin is an aminoglycoside, inhibiting the 30s subunit of the ribosome, preventing an incoming tRNA from binding to its codon within the A site. It was used to treat TB way back in the day, and is rarely used for TB now. It was the agent we first attempted to kill TB with. You will see it again in the treatment of MOTTS, below. If seen on an exam, it is almost certainly a distractor. Do not pick streptomycin for TB unless it is unmistakably obvious that it is multi-drug-resistant TB (which you shouldn't get, because that's Russia, not the US).

Other second-line agents are not discussed. They are too low yield. Multi-drug-resistant tuberculosis (MDR-TB) is a real thing. Advanced, complicated combination therapies are required where there is MDR-TB. Which means you should learn about those regimens if you are going to practice in an area that is endemic for MDR-TB. The United States is not one of those places. We didn't want to include these words, but a very high performer on Step 1 who reviewed our content told us we should at least write them down. We have spent more time convincing you that you should not read the next few words than it will take you to read them. Cycloserine, ethionamide, moxifloxacin, azithromycin, and bedaquiline. The sentence is incomplete on purpose.

Drugs that Treat *Mycobacterium leprae* (Leprosy)

Leprosy is separated into the Th1 immune response that contains the mycobacteria (tuberculoid leprosy) and the non-Th1 immune response that fails to contain the mycobacteria (lepromatous). Lepromatous is worse, so gets an extra drug. Both are treated with dapsone and rifampin; the lepromatous type adds clofazimine.

Dapsone is structurally related to sulfonamides, and inhibits dihydropteroate synthetase in the bacterial pathway for folate synthesis. Dapsone is also the second-line agent for PCP prophylaxis after trimethoprim/sulfamethoxazole (TMP/SMX; if not tolerated, dapsone; if not tolerated, atovaquone). Dapsone also exacerbates **G6PD deficiency** and provokes hemolysis, and can precipitate an aplastic anemia, just like sulfamethoxazole.

Rifampin is a rifamycin, discussed above.

Clofazimine is a phenazine dye, and the mechanism of action is not well understood. See dapsone and rifampin, and you know it's a leprosy regimen. If there is another agent added on, it's probably "that C drug," and the regimen is for lepromatous leprosy.

Drugs That Treat MOTTs

MOTTs are Mycobacteria Other Than Tuberculosis, and come down to MAC, leprosy (above), and some other things you really shouldn't learn.

Mycobacterium avium-intracellulare (MAI) is also known as *Mycobacterium avium* complex (**MAC**, which is easier to say than MAI, where people think you are saying the possessive "my" or are disappointed you don't follow it up with "tai.") Just like PCP, we encourage you to use the colloquial MAC. There are three presentations of this disease.

1. The first is a patient with AIDS whose CD4 < 50. They have no symptoms; they do not have the infection. They are given **prophylaxis** with **weekly azithromycin**.

2. The second is an AIDS patient with CD4 < 50 and diffuse lymphadenopathy. A biopsy confirms the infection with MAC, and it is treated with **azithromycin +** other stuff that looks like RIPE. For a really long time. You should see the presence of azithromycin as the clue that the regimen you are looking at on your exam is representing a regimen for MAC.

3. The third presentation is a patient who tests positive for AFB in a sputum sample. ACID-FAST POSITIVE!!!! START RIPE!!!!. They are started on RIPE for tuberculosis. Four weeks later at the second follow-up visit, you are informed that is actually not TB and is instead confirmed to be MAC. Pulmonary MAC is slow-growing, so it takes weeks to confirm. Because it is a *Mycobacterium*, the initial sputum sample and acid-fast stain were positive. A positive AFB smear, a positive acid-fast stain of a sample tells us only that it is a *Mycobacterium*. The patient is not infectious and can be taken off the toxic RIPE therapy, and treated for MAC instead.

310+: Other Mycobacteria

As if TB first-line agents, leprosy, and MAC weren't enough . . .

M. marinum is associated with people who have aquariums, and is treated with Isoniazid (+ B_6), rifampin, and ethambutol ← YAY! That is just RI_E.

M. ulcerans is none of the other mycobacteria, treated with rifampin and streptomycin. ← If you learn this you will confuse yourself.

A 310 is not possible on Step 1.